8. Traish AM, Park K, Dhir V, et al. Effects of castration and androgen replacement on erectile function in a rabbit model. *Endocrinology*. 1999;140:1861-1868.
9. Moreland RB, Traish A, McMillin MA, et al. PGE1 suppresses the induction of collagen synthesis by transforming growth factor-beta 1 in human corpus cavernosum smooth muscle. *J Urol*. 1995;153:826-834.
10. Jung GW, Kwak JY, Yoon S, et al. IGF-I and TGF-beta2 have a key role on regeneration of nitric oxide synthase (NOS)-containing nerves after cavernous neurotomy in rats. *Int J Impot Res*. 1999;11:247-259.
11. Dahiya R, Chui R, Perinchery G, et al. Differential gene expression of growth factors in young and old rat penile tissues is associated with erectile dysfunction. *Int J Impot Res*. 1999;11:201-206.
12. Lee MC, El-Sakka AI, Graziottin TM, et al. The effect of vascular endothelial growth factor on a rat model of traumatic arteriogenic erectile dysfunction. *J Urol*. 2002;167:761-767.
13. Rogers RS, Graziottin TM, Lin CS, et al. Intracavernosal vascular endothelial growth factor (VEGF) injection and adeno-associated virus-mediated VEGF gene therapy prevent and reverse venogenic erectile dysfunction in rats. *Int J Impot Res*. 2003;15:26-37.
14. Hood JD, Meininger CJ, Ziche M, et al. VEGF upregulates ecNOS message, protein, and NO production in human endothelial cells. *Am J Physiol*. 1998;274:H1054-H1058.
15. van der Zee R, Murohara T, Luo Z, et al. Vascular endothelial growth factor/vascular permeability factor augments nitric oxide release from quiescent rabbit and human vascular endothelium. *Circulation*. 1997;95:1030-1037.
16. Burchardt M, Burchardt T, Chen MW, et al. Expression of messenger ribonucleic acid splice variants for vascular endothelial growth factor in the penis of adult rats and humans. *Biol Reprod*. 1999;60:398-404.
17. Liu X, Lin CS, Graziottin T, et al. Vascular endothelial growth factor promotes proliferation and migration of cavernous smooth muscle cells. *J Urol*. 2001;166:354-360.
18. Rajasekaran M, Kasyan A, Jain A, et al. Altered growth factor expression in the aging penis: the Brown-Norway rat model. *J Androl*. 2002;23:393-399.
19. Park K, Ahn KY, Kim MK, et al. Intracavernosal injection of vascular endothelial growth factor improves erectile function in aged rats. *Eur Urol*. 2004;46:403-407.
20. Mills TM, Wiedmeier VT, Stopper VS. Androgen maintenance of erectile function in the rat penis. *Biol Reprod*. 1992;46:342-348.
21. Muller SC, Hsieh JT, Lue TF, et al. Castration and erection. An animal study. *Eur Urol*. 1988;15:118-124.
22. Mills TM, Lewis RW, Stopper VS. Androgenic maintenance of inflow and Veno-occlusion during erection in the rat. *Biol Reprod*. 1998;59:1413-1418.
23. Nehra A, Goldstein I, Pabby A, et al. Mechanisms of venous leakage: a prospective clinicopathological correlation of corporeal function and structure. *J Urol*. 1996;156:1320-1329.
24. Moreland RB. Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the society for the Study of Impotence. *Int J Impot Res*. 1998;10:113-120.
25. Siroky MB, Azadzoi KM. Vasculogenic erectile dysfunction: newer therapeutic strategies. *J Urol*. 2003;170:S24-S29; [Discussion: S9-30].
26. Ruohola JK, Valve EM, Karkkainen MJ, et al. Vascular endothelial growth factors are differentially regulated by steroid hormones and antiestrogens in breast cancer cells. *Mol Cell Endocrinol*. 1999;149:29-40.
27. Haggstrom S, Lissbrant IF, Bergh A, et al. Testosterone induces vascular endothelial growth factor synthesis in the ventral prostate in castrated rats. *J Urol*. 1999;161:1620-1625.
28. Sordello S, Bertrand N, Plouet J. Vascular endothelial growth factor is up-regulated in vitro and in vivo by androgens. *Biochem Biophys Res Commun*. 1998;251:287-290.
29. Kurz B, Lemke AK, Fay J, et al. Pathomechanisms of cartilage destruction by mechanical injury. *Ann Anat*. 2005;187:473-485.
30. Pufe T, Kurz B, Petersen W, et al. The influence of biomechanical parameters on the expression of VEGF and endostatin in the bone and joint system. *Ann Anat*. 2005;187:461-472.

EDITORIAL COMMENT

Penile erection is a complex neurovascular phenomenon that depends on the balance and integration of multiple overlapping control systems, including neurotransmitters, vasoactive agents, and endocrine factors. The link between testosterone (depletion and supplementation) and erectile function has been extensively studied in preclinical research. Nevertheless, considerable gaps in our understanding of these interactions remain to be elucidated. In either surgically or medically castrated animal models, it has been demonstrated that androgen deprivation results in a significant reduction in trabecular smooth muscle content and a marked increase in connective tissue deposition in the corpus cavernosum.[1] These changes ultimately lead to impaired sinusoidal expandability and thus corporeal veno-occlusive dysfunction (CVOD).[2] Other changes that have been observed in orchiectomized animals include the accumulation of adipocyte-like cells in the subtunical regions of the corpus cavernosum[3] and structural changes in the penile nerves.[4]

In this study, the authors elucidate in an elegant fashion one of the missing links in our understanding of how androgens are involved in the regulation of penile erection.[5] They demonstrate the critical role testosterone plays in regulation of penile vascular endothelial growth factor (VEGF) expression on both transcriptional (mRNA) and translational (protein) levels. The authors suggest that VEGF is expressed by endothelial cells lining the sinus; however, when reviewing the histology figure, the multilayered aspect of the stained perisinusoidal cells (Fig. 1A in[5]) suggests that expression may be present in the subendothelial cavernous smooth muscle. Thus, in addition to the conclusions drawn by the authors, VEGF may further play a role in maintenance of smooth muscle content and function. The specific tissue and cell types regulated by VEGF need to be further investigated in future research. Furthermore, erectile function is significantly compromised 1 week postcastration and returns to normal after 1 week of androgen replacement. Because these intervals are rather short, this raises the question of whether trophic changes induced by VEGF are the capital pathway of the effects of testosterone replacement on erectile function, or whether direct functional effects of androgens possibly play an additional role.

Rogers et al previously reported that both VEGF and VEGF gene therapy in castrated rats prevented and reversed venogenic erectile dysfunction as illustrated by an increased response to papaverine injection and a significantly decreased venous leakage.[2] In the latter study, VEGF (gene) therapy resulted in recovery of endothelial, neural, and smooth muscle structure, and decreased penile fibrosis after castration. These results replicate those found in studies using testosterone supplementation in castrated animals.[6]

Thus, it is becoming increasingly apparent that androgens regulate and maintain penile structure and function at least partially through interference with paracrine signaling in the erectile tissue. Of note, however, is that castration in rodents produced demonstrable changes in penile structure and reduced erectile function. This may be attributed to the fact that the rodents' adrenal glands do not produce sufficient androgen.[7] Translation of these results to the human should therefore be

done with caution. As the authors mention, further studies are required to fully understand the complex interactions between androgens and paracrine signaling in the erectile tissue.

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References

1. Traish AM, Munarriz R, O'Connell L, et al. Effects of medical or surgical castration on erectile function in an animal model. *J Androl*. 2003;24(3):381-387.
2. Rogers RS, Graziottin TM, Lin CS, et al. Intracavernosal vascular endothelial growth factor (VEGF) injection and adeno-associated virus-mediated VEGF gene therapy prevent and reverse venogenic erectile dysfunction in rats. *Int J Impot Res*. 2003;15:26-37.
3. Traish AM, Kim N. Weapons of penile smooth muscle destruction: androgen deficiency promotes accumulation of adipocytes in the corpus cavernosum. *Aging Male*. 2005;8(3-4):141-146.
4. Baba K, Yajima M, Carrier S, et al. Effect of testosterone on the number of NADPH diaphorase-stained nerve fibers in the rat corpus cavernosum and dorsal nerve. *Urology*. 2000;56(3):533-538.
5. Hwang EC, Oh KJ, Jung SI, et al. Effects of androgen on the expression of vascular endothelial growth factor in the penile corpus cavernosum. *Urology*. 2011;77(6):1381-1387.
6. Traish AM, Park K, Dhir V, et al. Effects of castration and androgen replacement on erectile function in a rabbit model. *Endocrinology*. 1999;140(4):1861-1868.
7. Traish AM, Guay AT. Are androgens critical for penile erections in humans? Examining the clinical and preclinical evidence. *J Sex Med*. 2006;3(3):382-404.

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